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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|-------------|----------------------|---------------------|------------------|
| 10/519,356 | 12/28/2004 | Bertram Cezanne | MERCK-2952 | 4530 |
| 23599 | 7590 | 04/20/2006 | EXAMINER | |
| MILLEN, WHITE, ZELANO & BRANIGAN, P.C. 2200 CLARENDON BLVD. SUITE 1400 ARLINGTON, VA 22201 | | | KOSACK, JOSEPH R | |
| | | | ART UNIT | PAPER NUMBER |
| | | | 1626 | |

DATE MAILED: 04/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) |
|------------------------------|------------------------|---------------------|
| | 10/519,356 | CEZANNE ET AL. |
| Examiner | Art Unit | |
| Joseph Kosack | 1626 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 17 February 2006.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-44 is/are pending in the application.
4a) Of the above claim(s) 4,5 and 32 is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 27,28,31 and 33 is/are rejected.

7) Claim(s) 1-3,6-26,29,30 and 34-44 is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892) 4) Interview Summary (PTO-413)
2) Notice of Draftsperson's Patent Drawing Review (PTO-948) Paper No(s)/Mail Date. ____ .
3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 12/28/2004.
5) Notice of Informal Patent Application (PTO-152)
6) Other: ____ .

DETAILED ACTION

Claims 1-44 are pending in the instant application.

Amendments

The amendment to the claims filed on February 17, 2006 has been acknowledged and has been entered into the record.

Election/Restriction

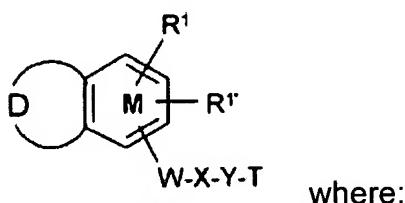
Applicant's election with traverse of Group I in the reply filed on February 17, 2006 is acknowledged. Applicant's arguments have been considered, but were not found persuasive.

The requirement is still deemed proper and is therefore made FINAL.

Status of the Claims

Claims 1-44 are pending in the instant application. Claims 1-3 (in part), 4-5, 6-31 (in part), 32, and 33-44 (in part) are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. The withdrawn subject matter is patentably distinct from the elected subject matter as it differs in the structure and element and would require separate search considerations. In addition, a reference, which anticipates one group, would not render obvious the other.

Pursuant to Applicant's election of a single compound, the scope of the invention will be limited to the following substitutions of the base structure



- D is absent;
- M is a phenyl ring;
- W is pyrazole attached to the M-phenyl ring via the 1 position;
- R¹ is -CH₂NH₂ attached meta to the pyrazole ring;
- X is CONH attached in the 5 position of the pyrazole ring;
- All other substituents are as defined.

As a result of the election and the corresponding scope of the invention defined

supra, the remaining subject matter of Claims 1-44 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to non-elected inventions.

The withdrawn compounds contain varying functional groups such as pyrimidinyl, piperidinyl, imidazoyl, pyrrolidinyl, etc, which are chemically recognized to differ in structure and function. This recognized chemical diversity of the functional groups can be seen by the various classification of these functional groups in the U.S. classification system, i.e. class 544 subclass 244(+) (diazines), class 546 subclass 184(+) (piperidines), 546 subclass 249(+) (pyridines), etc. Therefore the subject matter which are withdrawn from consideration as being non-elected subject matter differ materially in structure and composition and have been restricted properly a reference which anticipated but the elected subject matter would not even render obvious the withdrawn subject matter and the fields of search are not co-extensive. The non-elected subject matter also would have a different core structure than listed above, resulting in a different special technical feature and a lack of unity of invention.

Priority

The claim to priority as a 371 filing of PCT/EP03/05898 filed on June 5, 2003 which claims priority to DE 10229070.p filed on June 28, 2002 has been acknowledged in the instant application.

Information Disclosure Statement

The Information Disclosure Statement filed on December 28, 2004 has been considered by the Examiner. However, References 004 and 005 on the Information Disclosure Statement have not been considered in that they are not in compliance with MPEP 609 and 37 CFR 1.98 for failure to provide a copy of the publication or the portion of the publication which caused it to be listed. All other references cited have been considered fully by the examiner.

Claim Objections

Claims 1-3, 6-31, and 33-44 are objected to for containing elected and non-elected subject matter. The elected subject matter have been identified *supra*.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-28, 31, and 33 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating thromboembolic disorders such as thrombosis and myocardial infarction, does not reasonably provide enablement for treating other diseases such as tumors and inflammation. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The Nature of the Invention

The nature of the invention is the inhibition of coagulation factors Xa (Claim 27) and VIIa (Claim 28) and the treatment of specific diseases such as thromboses, myocardial infarction, and tumors without (Claim 31) and with an additional agent (Claim 33).

The State of the Prior Art and the Predictability or Lack Thereof in the Art

The state of the prior art is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Wong et al. (*Cardiovascular Drug Reviews* 2002, 137-152) teach a compound that is structurally similar to the compounds of Formula I of the instant application as an inhibitor of coagulation factor Xa. Wong et al. only teach the connection between factor Xa to treating acute myocardial infarction, unstable angina, deep vein thrombosis, pulmonary embolism, and ischemic stroke. Sampson et al. (*Biochemical Society Transactions* 2002, 201-207) teach the role of factors VIIa and Xa in the blood coagulation cascade, but does not give any information on the importance of those specific factors in treating cancer, inflammation, or other diseases not associated with thrombosis. Schulman et al. (*New England Journal of Medicine* 2000, 1953-1958) teach that the beneficial effects of treatment of small-cell lung cancer with the anticoagulant warfarin in a 1981 clinical trial have never been confirmed. Schulman et al. also teach that the addition of warfarin to treatment of small-cell lung cancer to a regimen of chemotherapy and radiation resulted in no improvement over chemotherapy and radiation alone.

Hence, in the absence of a showing of correlation between all the diseases claimed as capable of treatment by inhibiting coagulation factors VIIa and Xa, one of skill in the art is unable to fully predict possible results from the administration of the

compound of formula 1 due to the unpredictability of the role of inhibiting coagulation factors VIIa and Xa with respect to diseases other than thromboembolic disorders.

The Amount of Direction or Guidance Present and the Presence or Absence of Working

Examples

The specification teaches the positive effects of inhibiting coagulation factors VIIa and Xa in treating thromboembolic disorders. The specification also cites certain references describing the antitumoral action of tissue factor TF/ factor VIIa and factor Xa inhibitors for various types of tumor. However, upon closer inspection of the cited teachings of Bromberg et al. (*Thrombosis and Haemostasis* 1999, 88-92.) no inhibitors of TF/VIIa were attempted, let alone the effects of a small molecule inhibitor of factor VIIa on the treatment of tumors. An example shows binding affinity to factors Xa and TF/VIIa of four compounds of the instant invention, but nothing is shown as to how the treatment of tumors can be accomplished. Also, it is unknown who the target population is for the method of inhibiting coagulation factors Xa and VIIa. As the claims read currently, it is believed that the target population is any living being since there is no definition of the patient population in the disclosure.

The Breadth of the Claims

The breadth of the claims is the the inhibition of coagulation factors Xa (Claim 27) and VIIa (Claim 28) of any living being and the treatment of specific diseases such as thromboses, myocardial infarction, and tumors without (Claim 31) and with an additional agent (Claim 33).

The Quantity of Experimentation Needed

The quantity of experimentation for the general inhibition of factors Xa and VIIa in a patient and for the treatment of diseases other than thromboembolic disorders needed is undue experimentation. As to general inhibition of factors Xa and VIIA, one of ordinary skill in the art would have to determine what the patient population is that would benefit from the inhibition of those factors. Because of the uncertainty in the art to the treatment of diseases other than thromboembolic disorders with anticoagulants and factor Xa and VIIa inhibitors, undue experimentation would be necessary to test the efficacy of a method of treatment.

The Level of Skill in the Art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound of formula 1 for the general inhibition of factors Xa and VIIa in a patient and for treating diseases other than thromboembolic disorders. As a result, necessitating one of skill to perform an exhaustive search for the proper patient population and any diseases other than thromboembolic disorders that can be treated by what compounds of formula 1 in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

This rejection can be overcome deleting the claims or by deleting the non-enabled portions of the method claims.

Conclusion

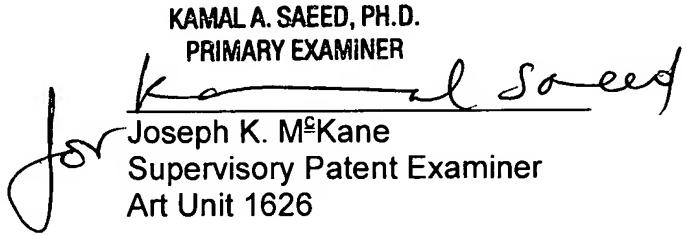
Claims 27-28, 31, and 33 are rejected. Claims 1-3, 6-31, and 33-44 are objected to. Claims 1-3, 6-31, and 33-44 are free of the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Kosack whose telephone number is (571)-272-5575. The examiner can normally be reached on M-F 7:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph M^cKane can be reached on (571)-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


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